

PCT/ LB 2004/ 003092

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THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Provisional Specification filed on 26.09.2003 of the extract of Patent Application No. 789/CHE/2003 by M/S National Centre for Biological Sciences , Tata Institute of Fundamental Research, UAS-GKVK Campus, Bellary Road, Bangalore-560 065, Karnataka, India, an Indian Company.

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

.....In witness thereof

I have hereunto set my hand

Dated this the 25th day of October, 2004
3rd day of Kartica, 1926 (Saka)

M. S. Venkataraman

(M.S.VENKATARAMAN)

ASSISTANT CONTROLLER OF PATENTS & DESIGNS

[Signature]

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 4th Floor, Annex.II
No.443, Anna Salai, T. Nagar, Chennai - 600 004

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2000/- 26/04
 int. C.A.R. No. 6670
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$$\overline{26} \overline{)9}$$

1. I/We,

(a) National Centre for Biological Sciences
Tata Institute of Fundamental Research
UAS-GKVK Campus
Bellary Road
Bangalore – 560 065
2. hereby declare –
 - a) that we are in possession of an invention titled
“Novel conotoxin from an Indian marine snail”
 - b) that a provisional specification relating to this invention is filed with this application.
 - c) that there is no lawful ground of objection to the grant of a patent to us.
3. Further declare that the inventor(s) of the said invention are
 1. Prof. K. S. Krishnan, National Centre for Biological Sciences, Tata Institute of Fundamental Research, Bangalore – 560 065, an Indian National
 2. Prof. P. Balaram, Indian Institute of Science, Bangalore – 560 012, an Indian National
4. We claim the priority from the application(s) filed in convention countries particulars of which are as follows:
 - a) Not applicable
 - b) Not applicable
 - c) Not applicable
 - d) Not applicable
5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant / patentee:
 - a) Not applicable
 - b) Not applicable
 - c) Not applicable

ORIGINAL 26 SEP 2003



6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on this fifteenth day of September 2003, under section 16 of the Act

- a) Not applicable
- b) Not applicable
- c) Not applicable

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

Senior Administrative Officer
National Centre for Biological Sciences
Tata Institute of Fundamental Research
UAS-GKVK Campus, Bellary Road
Bangalore – 560 065

Ph: +91-80-3636729
Email: tms@ncbs.res.in

9. Following declaration was given by the inventor(s) or applicants(s) in the convention country:

I/We, the true and first inventor(s) for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is our assignee or legal representative.

Prof. P. BALARAM

P. Balaram

Prof. K. S. KRISHNAN

10. That to the best of our knowledge, information and belief that fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. The following are the attachments with the application:

- a. Provisional specification in triplicate on Form 2 - 2 copies
- b. Statement & undertaking on Form 3
- c. Demand draft of the Central Bank of India for Rs.3,000/- (Rupees Three Thousand only) bearing No.029323 dated 26th September 2003 drawn on Chennai.

[Signature]

Fee Rs.3,000/- (Rupees Three Thousand only) vide demand draft bearing No.029323 dated 26th September 2003 drawn on Chennai.

We request that a patent may be granted to us for the said invention.

Dated this twenty fifth day of September 2003.



K. VijayRaghavan
Centre Director
NCBS-TIFR

To
The Controller of Patents
The Patent Office
CHENNAI

Prof. K. VijayRaghavan
Centre Director
National Centre for Biological Sciences
Tata Institute of Fundamental Research
GKVK Post, Bangalore - 560 065

Novel conotoxins from an Indian marine snail

National Centre for Biological Sciences, Tata Institute of Fundamental Research, UAS-GKVK Campus, Bangalore – 65.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION:

(see Section 10)

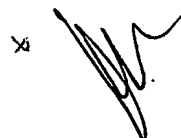
Novel conotoxins from an Indian marine snail.

We, National Centre for Biological Sciences, Tata Institute of Fundamental Research,
UAS-GKVK Campus, Bangalore – 560 065, INDIA

The following specification particularly describes and ascertains the nature of this invention:

Field of invention

This invention relates to the field of novel conotoxin from an Indian marine snail for therapeutic application in human medicine.



12/10/03

789 / CHE/2003

ORIGINAL 26 SEP 2003

Novel conotoxins from an Indian marine snail

National Centre for Biological Sciences, Tata Institute of Fundamental Research, UAS-GKVK Campus, Bangalore - 65.

Prior art

Conotoxins, a group of pharmacologically active peptides produced by diverse species of conus snails, act with a high degree of specificity on different classes of channels and receptors in excitable cells. The evolution of conotoxins in the venom of predator snails may be influenced by selective pressures imposed by the nature of the prey, with peptide mixtures from molluscivorous, piscivorous and vermivorous snails exhibiting differences. Systematic elucidation of structure-activity relationships for all components in a conotoxin mixture is impeded by the difficulties in isolating and identifying every individual peptide. Conotoxins are characterized by multiple disulfide bridges, which provide a relatively rigid peptide backbone framework, upon which amino acid side chains, important for interaction with the pharmacological receptors, are arrayed. The classification of conotoxins has relied on the distribution of Cys residues in the primary sequence, the nature of the disulfide pairing topology and the functional attributes of the peptides. As many as 14 classes of conotoxins have thus far been identified (α , αA , δ , ϵ , γ , κ , λ , λ/χ , μ , μO , ρ , σ , ω and ψ). The δ -conotoxins have been shown to inhibit voltage-gated Na^+ channel inactivation. The specific role of the peptide δ P VIA in combination with a K^+ channel antagonist κ P VIIA has been shown to be critical for prey capture in the fish-hunting snail, *Conus purpurascens*. Peptide combinations (cabals), which act in concert at distinct target sites, have been suggested to be important in rapid immobilization of prey. The δ -conotoxins identified thus far have polypeptide chain lengths of 27-32 amino acids and have three disulfide bridges with a pattern (1-4; 2-5; 3-6), where 1-6 indicates the six Cys residues starting from the N-terminus. The only other class of conotoxins characterized thus far that target Na^+ channels are the μ -conotoxins, which share a similar disulfide-bonding pattern, but have a relatively shorter polypeptide chain length of 17-22 amino acids. The isolation of δ -conotoxins from complex mixtures is rendered difficult due to their hydrophobicity.

As a part of the program to explore diversity of conotoxins produced by conus snail species found off the Indian coast, we report the isolation and characterization of a δ -conotoxin from *Conus amadis*, a hitherto uninvestigated species of snail collected in the Bay of Bengal. The conus peptide Am 2766 is shown to inhibit the delayed inactivation of a mammalian Na^+ channel.

NATURE OF INVENTION

In this patent we describe a 26 residue peptide with the sequence CKQAGESCDIFSQNCCVG-TCAFICIE-NH₂ that has been isolated and purified from the venom of the molluscivorous snail, *Conus amadis*, collected off the southeastern coast of India. Chemical modification and mass spectrometric studies establish that Am 2766 has

Novel conotoxins from an Indian marine snail


National Centre for Biological Sciences, Tata Institute of Fundamental Research, UAS-GKVK Campus, Bangalore - 65.

three disulfide bridges. C-terminal amidation has been demonstrated by mass measurements on the C-terminal fragments obtained by proteolysis. Sequence alignments establish that Am 2766 belongs to the δ -conotoxin family. Am 2766 inhibits the decay of the sodium current in brain rNav1.2a voltage-gated Na^+ channel, stably expressed in Chinese hamster ovary cells. Unlike δ -conotoxins have previously been isolated from molluscivorous snails, Am 2766 inhibits inactivation of mammalian sodium channels.

This peptide is likely to be very useful in the directed treatment of a range of neurophysiological and neurological disorders such as those seen in schizophrenia, epilepsy, bipolar disorder and in syndromes that affect the nervous system.

Dated this Twenty Fifth Day of September 2003.

To,
The Controller of Patents
The Patent Office
CHENNAI


Centre Director
NCBS-TIFR
Prof. K. VijayRaghavan
Centre Director
National Centre for Biological Sciences
Tata Institute of Fundamental Research
GKVK Post, Bangalore - 560 065

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